EXECUTIVE SUMMARY

Background

A large body of scientific evidence has established that particulate air pollution has detrimental cardiopulmonary effects on human health. Multiple studies have identified particles from motor vehicle combustion engines as having a particularly important impact on human health. Accordingly, regulatory and monitoring policies have been established to limit particulate matter (PM) levels in the ambient air. These air quality standards have been based on yearly or daily averages. However, previous studies have illustrated that short-term exposure to some types of PM can lead to adverse health effects. Thus, there is a need for increased understanding of how ambient PM may impact human health over short exposure time periods. Animal, cellular and human epidemiological studies all confirm that short-term exposure to PM can cause airway inflammation. However, human studies that have directly tested short-term PM exposure on human subjects have reported only modest, subtle changes in disease markers likely because of the great heterogeneity in responses observed. A few studies show that marked significant changes do occur but only in some subjects. Thus, it becomes important to study individuals with risk factors for susceptibility or responsiveness to PM. Based on available data, two prominent "susceptibility factors" (GSTM1 null genotype and asthma) have been selected for study. These susceptibility factors, specific genotype (presence of the *GSTM1* null polymorphism) and underlying pulmonary disease (asthma) are very common (50% and 8% respectively). By investigating these “at-risk” populations specifically, it is possible to determine the impact of PM on a large segment of the population which is potentially most vulnerable to the adverse health effects of air pollution. Such studies may allow future air quality regulations to not only protect the health of the general public, but to additionally protect the health of subpopulations at significantly greater risk. Additionally, this study will address a knowledge gap regarding the inflammatory effects of fine concentrated ambient particle (CAPS) exposure in susceptible subpopulations as previous similar work has predominantly focused on diesel exhaust particles (DEP). **The primary objective of this study is to test the hypothesis that individuals with certain ‘susceptibility factors’ will have heightened inflammatory and airway responses with exposure to concentrated ambient particles (CAPS).**

Methods

We conducted a single-blind randomized crossover study of controlled exposure to filtered air (FA) and to concentrated ambient fine particles (CAPS), in 10 GSTM1 null mild-moderate asthmatics, 10 GSTM1 positive mild-moderate asthmatics, and 10 GSTM1 positive healthy subjects. All human subject procedures were approved by the appropriate institutional review boards at Los Amigos Research & Education Institute (LAREI) and University of California, Los Angeles (UCLA). Each subject completed the study protocol with a total of 5 visits: 1 screening visit, 2 exposure days, and 2 follow up visits 1-day post-exposure. Experimental exposures were separated by at least 2 weeks. Each subject was exposed in a whole-body chamber to CAPS (PM2.5) at a target concentration of 200 $\mu g/m^3$ monitored in real time by a nephelometer and controlled by diluting the output of the ambient fine particle concentrator with varying amounts of filtered air. Exposures lasted two hours, with submaximal exercise (approximately tripling resting ventilation) for 15 min of every half-hour. Outcome measures included symptom scores,

physiologic measures (vital signs, spirometry, exhaled nitric oxide, heart rate variability) as well as serum, sputum, and nasal lavage samples for inflammatory biomarkers.

Results

Thirty-one subjects enrolled in the study and thirty subjects (10 GSTM1-null asthma subjects, 10 GSTM1-present asthma subjects, 10 GSTM1-present healthy subjects) completed the protocol. No serious adverse events occurred. Particle mass concentrations averaged 187$\mu g/m^3$ for CAPS and 35 $\mu g/m^3$for FA during the 2-hour exposures. Overall, few significant CAPS-attributable changes were observed for physiologic and symptom endpoints, consistent with findings in previous studies using similar exposures. An unequivocally significant relative increase in FeNO was associated with CAPS exposure for all groups, without significant changes in most concurrent respiratory or systemic inflammatory markers. Sputum total cell counts trended higher after CAPS than after FA exposures and nasal lavage IgG4 was increased after CAPS and decreased after FA exposure for the entire population. GSTM1-null asthmatics reported increased symptom scores during both CAPS and FA exposures. Post –exposure systolic blood pressure decreases were observed in all groups for both FA and CAPS exposures. Heart rate variability (HRV) data showed increased heart rate and decreased HRV post-exposure across all groups regardless of exposure conditions (CAPS or FA). CAPS exposure and susceptibility group showed minimal effects on HRV changes. Overall, some data supported the hypothesis of airway inflammatory responses to CAPS exposure, but these responses were not significantly different between subject groups. Thus, within the limitations of the study design, the data does not support the hypothesis that individuals with mild-moderate asthma or GSTM1-null genotype have increased susceptibility to the inflammatory effects of short-term CAPS exposure.

Conclusions

In summary, the study findings do not support the hypothesis that human subjects with mild-moderate asthma or GSTM1-null genotype have greater inflammatory responses to short-term CAPS exposure at levels approximating 200$\mu g/m^3$ for 2 hours. If such responses are influenced by asthma status and GSTM1 genotype, the influences appear to be subtle and were not detected by the instituted study design. Identification and characterization of subpopulations susceptible to the adverse health effects of particulate air pollution remains a critically important area of research. Based on our findings, future exposure study designs should consider factors of increased power from larger subject enrollment, potential alternatives to spirometric changes as primary study endpoints, increased CAPS exposure (higher concentration and/or greater duration), cautious and ethical inclusion of more clinically severe asthmatics in exposure studies, and consideration of additional genetic and host co-factors such as diet that may modulate inflammatory response to oxidative stress. Additionally, our current study data shows relative increases in FeNO with CAPS exposure suggesting potential utility of this measurement as an early sensitive marker of airway inflammatory responses to fine particle exposure in both healthy and asthmatic individuals. Inclusion of FeNO measurement in future fine CAPS exposures will be useful in determining the significance of this finding.